REMARKS

Claims 7, 11-13, 26 and 28-31 are pending in the application. Claims 12-13 are withdrawn. No claims are presently amended. Applicants respectfully request reconsideration of the present application in view of the revised declaration of Dr. Ingunn Holen, an experienced oncology researcher (Declaration ¶ 1), and the reasons that follow.

Claims 7, 11, 26 and 28-31 stand rejected as allegedly unpatentable under 35 U.S.C. 103(a) over Jagdev *et al.* (*British Journal of Cancer*, 2001, 84:1126-34). The Office asserts that "Since Jagdev already teaches that a combination of ZOL and PAC is synergistic for the treatment of breast cancer, it will be expected that any form of dosage of these two active ingredients, whether they are administered simultaneously (like Jagdev teaches) or sequentially (like in the instant Application) will still be synergistic. So there is nothing in the claims and/or specification that show any unexpected result based on what is disclosed and taught by Jagdev." Applicants respectfully submit that this analysis is not supported by the state of the art and ignores Applicant's evidence of surprising and unexpected results.

First, Applicants disagree with the Office's assertion that Jagdev teaches clinically relevant concentrations of ZOL. While Jagdev may disclose combinations of PAC and ZOL that include "ZOL concentrations below 10 micromolar like: 0.010 micromolar, 0.10 micromolar and 1 micromolar," Applicants dispute that such "can now be translated into an effective amount as recited by the instant claims." Office Action, p. 4, lines 13-16. Therapeutically effective amounts of a drug, as recited in the presently claimed methods, depend not only on achieving a particular concentration, but on the length of exposure to such a concentration. Exposure times will depend, as acknowledged by the Office, on "efficacy, toxicity and the pharmacokinetic properties of a particular drug." Id., lines 17-20. What the Office has not acknowledged is that ZOL has significant toxicity and a short half-life, making the 72 hour exposure times disclosed in Jagdev unrealistic for clinical use and making it impossible to predict whether the therapeutic effects observed after a 72 hour exposure may be obtained under clinical conditions.

As explained in Applicants' last response, due to well-known renal toxicity, acute phase reactions, and osteonecrosis of the jaw, ZOL is typically administered for cancer treatment in small carefully controlled doses widely spaced in time: e.g., by IV infusion for 15 minutes at a dose of 4 mg/patient no more often than once every 3-4 weeks. (See Diel *et al.* "Adverse Effects of Bisphosphonates," *J. Support. Oncol.* 5: 475-82, 2007 (previously submitted); and Declaration, ¶ 2.) Following IV infusion, ZOL is known to remain in the plasma for no more than a few hours before being excreted or localizing to the bone. (*Id.*) Hence, repeated and prolonged infusion periods of zoledronic acid would be required to reproduce the 72 hours exposure tested in the Jagdev reference and such an exposure is not achievable in clinical practice due to the toxicity of zoledronic acid. (*Id.*; see also "Neville-Webbe et al., "Sequence- and Schedule-Dependent Enhancement of Zoledronic Acid Induced Apoptosis by Doxorubicin in Breast and Prostate Cancer Cells," *Int. J. Cancer*, 2005, 113:364-71, 365 ("Exposure of MCF7 cells to zoledronic acid for 72 hr, while inducing significant apoptosis, is not achievable in vivo.").) By definition, if the concentrations and exposure time of the ZOL disclosed by Jagdev *et al.* are not clinically achievable, they are not an effective amount as recited by the claimed methods and it was not predictable whether a much shorter exposure time would produce the same synergistic effects.

Thus, it is simply not accurate to assert that "even if the above concentrations had not been disclosed, the [sic] skilled in the art would have been able to adjust any *in vitro* regimen to an *in vivo* regimen according to efficacy, toxicity and the and [sic] pharmacokinetic properties of a particular drug, and thus obtain an efficacious dose regimen." (Office Action, p. 4, lines 17-20.) For example, as shown in a paper by several of the inventors, zoledronic acid in combination with doxorubicin did not show a statistically significant increase in apoptosis in MCF7 breast cancer cells when given together or when zoledronic acid was given followed by doxorubicin. Neville-Webbe *et al.*, p. 366 (text and Figure 3). Only when doxorubicin was administered first, followed by zoledronic acid were synergistic results achieved. *Id.* Hence, in this example, it does not appear possible to adjust the results obtained with one sequence of administration to the reverse sequence or concomitant administration of the combination of

drugs. While the objective of the skilled artisan may be to translate an *in vitro* regimen into an *in vivo* regimen, where as here, there are good reasons to doubt the predictability of such a translation, there can be no assurance of the desired outcome. In the face of such unpredictability, Applicant's methods and results cannot be considered obvious.

In view of such considerations, the skilled artisan will understand that the 1 hour exposure times of cells to ZOL disclosed in the application is therefore far closer to what happens in the clinic than the 72 hour exposure employed by Jagdev. (See also, Declaration, ¶ 4.) This is important as ZOL is typically administered to a cancer patient in short (15 minute) IV infusions spaced at least 3-4 weeks apart. (Declaration, ¶ 3.) As noted above, after such an infusion, ZOL localizes to the bone or is excreted and therefore cancer cells (such as breast cancer cells) are exposed to ZOL only briefly. The fact that an exposure time for ZOL of only 1.3% as long as that used in the prior art reference still resulted in a synergistic effect is surprising, not predictable and demonstrates proof of principle for this clinically relevant exposure time. (Declaration, ¶ 5.)

Applicants also disagree with the Office's assertion that the synergism disclosed by Jagdev is "very close to the synergism claimed by Applicant," and "the skilled in the art would definitively adjust the timing of the dose according to a patent requirement." (Office Action, p. 5, lines 8-20.) As acknowledged by the Office, Applicants' sequential administration of PAC and ZOL demonstrate a 16-fold increase in apoptosis of breast cancer cells compared to ZOL alone, while Jagdev's protocol achieved only 5-fold. As this is more than a 300% increase in efficacy in this experiment, this is clearly a surprising and unexpected result. The Office has provided no evidence that this result could have been predicted based on the disclosure of Jagdev in view of the limited half-life and known toxicity of ZOL. While the skilled artisan may desire to adjust the timing of a drug dose to avoid toxic effects, that does not mean there is a reasonable expectation of success in doing so.

Finally, Applicants again dispute the Office's assertion that "there is essentially no limitation on the concentrations of any of the active agents," and that Applicant's results "would

not be unexpected based on the teachings of Jagdev." By definition, a therapeutically effective amount of an agent is one which is, in fact, effective and which must be achievable in practice. A drug dose which is so low as to have no effect cannot be therapeutically effective and is excluded from the claims. Likewise, a drug dose which is too toxic to use cannot be therapeutically effective because it is too high to actually use in a subject. Thus, "therapeutically effective amount" is a commonly used term of art that definitely sets limits on the amounts an agent to be used in the present methods. Moreover, with respect to PAC and ZOL, it is already known what the toxicities of these two compounds are and therefore the upper limit for dosing. Applicants have demonstrated a range of lower doses which are synergistic and which, contrary to the Office's analysis, could not have been predicted to be synergistic based on the much longer exposure times of Jagdev. Accordingly, Applicants respectfully request withdrawal of the present ground of rejection.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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